American Journal of Medical Genetics 65:363–365 (1996)

Letter to the Editor

Phacomatosis Pigmentokeratotica: A Melanocytic-Epidermal Twin Nevus Syndrome

To the Editor:

In recent years it has been generally recognized that there is no such clinical entity as "the epidermal nevus syndrome." Rather, this designation can be applied to a group of several distinct phenotypes [Happle, 1991]. Here we propose to delineate a further separate type of epidermal nevus syndrome and to explain it by the genetic mechanism of twin spotting.

Recently, we observed a girl affected with a verrucous epidermal nevus of a nonepidermolytic type and a contralateral mosaic area covered with lentiginous and papular melanocytic lesions (Fig. 1) [Tadini et al., 1995]. Meanwhile, a thorough review of the literature showed the existence of 7 similar cases (Table I). For the following reasons it seems worthwhile to consider the delineation of a new entity for which we propose the name *phacomatosis pigmentokeratotica.*

First, twin spotting is a well-recognized mechanism that manifests itself rather frequently in plants and animals [Vig and Paddock, 1970; Graf et al., 1984] and was recently suggested to occur also in human skin [Happle et al., 1990]. Twin spots are paired patches of mutant tissue that differ from each other and from the background tissue [Whitehouse, 1982]. In an embryo heterozygous for two different recessive mutations localized on the same chromosome, an event of somatic crossing-over may give rise to two homozygous daughter cells representing the stem cells of two different mutant patches. The unusual co-occurrence of an epidermal nevus of the nonepidermolytic, organoid type, and a speckled lentiginous nevus of the papular type may be best explained by a similar mechanism. The term phacomatosis pigmentokeratotica has been chosen in analogy to phacomatosis pigmentovascularis, a phenotype that has likewise been explained as a possible example of twin spotting [Happle and Steijlen, 1989].

Second, in six of the cases summarized in Table I the two different types of nevi were found either in adjacent areas or in corresponding regions on either side of the body, suggesting a common origin from a somatic mutational event. Remarkably, Misago et al. [1994] had already speculated on "some common mechanism" in order to explain the temporal and spatial proximity of a speckled lentiginous nevus and sebaceus nevus as observed in their case and that of Kopf and Bart [1980].

Third, one of these patients had, in addition, a diffuse ichthyosis-like hyperkeratosis involving the entire body [Tadini et al., 1995]. This finding lends support to the assumption that her epidermal nevus originated from loss of heterozygosity by somatic recombination. This nevus would reflect homozygosity for a mutation that gives rise, in a heterozygous state, to mild diffuse hyperkeratosis. Remarkably, clinical photographs published in another report [Brufau et al., 1986] suggest the presence of a similar diffuse ichthysis-like hyperkeratosis, although this finding was not mentioned in that article.

Fig. 1. Phacomatosis pigmentokeratotica showing a predominantly unilateral arrangement of speckled lentiginous nevus and contralateral systematized verrucous epidermal nevus. Note habitual deviation of posture. Girl, age 11 years [for a detailed report of this case see Tadini et al., 1995].

Received for publication August 28, 1995; revision received December 19, 1995.

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TABLE I. Synopsis of Reports on Co-Occurring Speckled Lentiginous Nevus and Epidermal Nevus

Reference	Sex	Age (years)	Localization of speckled lentiginous nevus	Localization of epidermal nevus	Associated anomalies
Wauschkuhn and Rohde, 1971	M	5	Arm (left side)[a]	Head and neck (both sides), leg (right side)	Epileptic seizures, waddling gait; paresis of hand and leg (right side); hemihypoplasia of pelvis (left side)
Stein et al., 1972	M	13	Trunk and arms (both sides)	Scalp, ear and periauricular region (right side)	Bony asymmetry of the body, the right side being smaller than the left. Ptosis of the left eyelid, disturbance of eye movements, internal strabismus; muscular weakness of the face and the limbs (right side); conductive hearing loss (both sides)
Kopf and Bart, 1980	F	18	Temporozygomatic region (right side)	Scalp and periauricular region (right side)	—
Brufau et al., 1986 (case 1)	F	45	Trunk and arm (right side)	Trunk and leg (left side)	Pigmented spot on sclera of left eye; kyphoscoliosis; diffuse ichthyosis-like hyperkeratosis[b]
Brufau et al., 1986 (case 6)	M	6	Face and neck (left side)	Neck (right side)	Habitual bent posture with deviation to the left
Goldberg et al., 1987	F	33	Head, neck, trunk and limbs (right side)	Head, neck and trunk (left side)[c]	Joint laxity of the hand, muscular weakness of arm and shoulder girdle (right side); internal strabismus; palsy of 6th and 7th cranial nerves, multiple basal cell epitheliomas originating from sebaceous nevus (left side); thoracic kyphosis, lumbar lordosis
Misago et al., 1994	M	26	Preauricular and malar region (right side)	Preauricular and malar region (right side)	Basal cell epithelioma originating from sebaceous nevus
Tadini et al., 1995	F	9	Neck, trunk and arm (left side)[a]	Trunk and arm (right side)	Diffuse ichthyosis-like hyperkeratosis; habitual deviation of posture with bending of right arm; abnormal EEG (right side)

[a] Some additional melanocytic lesions involved other areas of the body.
[b] Documented on photographs, but not mentioned in text.
[c] Some small lesions of sebaceous nevus were also present in the right head and neck region.

The melanocytic component of the twin nevi can be categorized as speckled lentiginous nevus of a papular type. Stein et al. [1972] have published their case as an example of "neurofibromatosis in the pretumor stage" but we think that this diagnosis is not appropriate and should be changed into phacomatosis pigmentokeratotica.

In some cases the epidermal nevus showed, in those parts that involved the head, a hyperplasia of sebaceous glands consistent with a sebaceous nevus [Wauschkuhn and Rohde, 1971; Kopf and Bart, 1980; Goldberg et al., 1987; Misago et al., 1994]. Apparently, the epidermal component of phacomatosis pigmentokeratotica turns out to be identical with that of Schimmelpenning syndrome that has so far two different entries (MIM number 163200 and 165630) in McKusick's catalog [1994]. However, so far the pattern of extracutaneous anomalies observed in phacomatosis pigmentokeratotica appears to be at variance with a unifying concept. In particular, coloboma or lipodermoid of the conjunctiva as observed in Schimmelpenning syndrome have so far not been found to be associated with phacomatosis pigmentokeratotica. Alternatively, the term "sebaceous nevus syndrome" would no longer be unambiguous because it would apply to two different clinical entities. In either case, the concept of phacomatosis pigmentokeratotica implies the new aspect that the associated epithelial nevus does not reflect a heterozygous but rather a homozygous state of the underlying gene.

In three further cases, an unusual association of sebaceous nevus with vitamin D–resistant rickets and ipsilateral arrangement of multiple melanocytic nevi of various categories and sizes has been reported [Sugarman and Reed, 1969; Aschinberg et al., 1977; Goldblum and Headington, 1993]. These cases may likewise represent a twin spotting phenomenon but their nosological classification so far remains unclear.

Table I shows that phacomatosis pigmentokeratotica is associated with characteristic extracutaneous anomalies. In particular, neurological abnormalities appear to be a typical component of this syndrome. In six of the cases a deviation of posture or other neurological or skeletal signs of asymmetry were noted.

All of the cases of phacomatosis pigmentokeratotica observed so far have been sporadic. Apparently, at least one of the two underlying genes represents a lethal mutation that survives by mosaicism [Happle, 1993].

In conclusion, it seems likely that the co-occurrence of speckled lentiginous nevus of a papular type and epidermal nevus of a nonepidermolytic, organoid type constitutes a distinct syndrome reflecting twin spotting. Future clinical and molecular research should show whether this concept holds true.

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